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RESEARCH ARTICLE

Stiff person spectrum disorder diagnosis, misdiagnosis, and suggested diagnostic criteria

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Abstract

Background: Stiff person spectrum disorder (SPSD) is heterogeneous, and accurate diagnosis can be challenging. **Methods**: Patients referred for diagnosis/suspicion of SPSD at the Mayo Autoimmune Neurology Clinic from July 01, 2016, to June 30, 2021, were retrospectively identified. SPSD diagnosis was defined as clinical SPSD manifestations confirmed by an autoimmune neurologist and seropositivity for high-titer GAD65-IgG (>20.0 nmol/L), glycine-receptor-IgG or amphiphysin-IgG, and/or confirmatory electrodiagnostic studies (essential if seronegative). Clinical presentation, examination, and ancillary testing were compared to differentiate SPSD from non-SPSD. **Results**: Of 173 cases, 48 (28%) were diagnosed with SPSD and 125 (72%) with non-SPSD. Most SPSD were seropositive (41/48: GAD65-IgG 28/41, glycine-receptor-IgG 12/41, amphiphysin-IgG 2/41). Pain syndromes or functional neurologic disorder were the most common non-SPSD diagnoses (81/125, 65%). SPSD patients more commonly reported exaggerated startle (81% vs. 56%, $p = 0.02$), unexplained falls (76% vs. 46%, $p = 0.001$), and other associated autoimmunity (50% vs. 27%, $p = 0.005$). SPSD more often had hypertonia (60% vs. 24%, $p < 0.001$), hyperreflexia (71% vs. 43%, $p = 0.001$), and lumbar hyperlordosis (67% vs. 9%, $p < 0.001$) and less likely functional neurologic signs (6% vs. 33%, $p = 0.001$). SPSD patients more frequently had electrodiagnostic abnormalities (74% vs. 17%, $p < 0.001$), and at least moderate symptomatic improvement with benzodiazepines (51% vs. 16%, $p < 0.001$) or immunotherapy (45% vs. 13% $p < 0.001$). Only 4/78 non-SPSD patients who received immunotherapy had alternative neurologic autoimmunity. **Interpretation**: Misdiagnosis was threefold more common than confirmed SPSD. Functional or non-neurologic disorders accounted for most misdiagnoses. Clinical and ancillary testing factors can reduce misdiagnosis and exposure to unnecessary treatments. SPSD diagnostic criteria are suggested.

Introduction

Stiff person syndrome (SPS), first described in 1956, is a rare autoimmune disorder characterized by central nervous system (CNS) hyperexcitability presenting with limb and truncal muscle stiffness and spasms and exaggerated startle responses.[1–5] There is a wide range of clinical presentations from limited forms such as stiff-limb syndrome to additional neurologic features such as ataxia, epilepsy, or progressive encephalomyelitis with rigidity and myoclonus (PERM) leading to increasing use of the term stiff person spectrum disorder (SPSD).[2,6,7]

Diagnosis is based on clinical presentation, electrophysiological evidence, and antibody testing.[8] Patients are most commonly seropositive for GAD65-IgG at high titers.[2,9–12] Other associated neural antibodies with SPSD and CNS hyperexcitability disorders are specific for the glycine receptor alpha-1-subunit (GlyR-IgG) and amphiphysin and more rarely dipeptidyl-peptidase-like protein-6 (DPPX-IgG), gephyrin, glycine transporters, γ-aminobutyric acid-A receptor ($GABA_AR$), and possibly GABA-receptor-associated protein (GABARAP).[7,13–22] A minority of patients are seronegative for known antibodies. Electrodiagnostic studies can show excessive muscle activation with acoustic startle or exteroceptive stimulus, or presence of continuous paraspinal or agonist/antagonist muscle activity with electromyography (EMG).[5,8,23,24]

SPSD diagnosis is often delayed.[4,25] To date, issues relating to SPSD diagnosis have focused on missing the diagnosis.[26–28] However, we have identified many patients with alternative diagnoses misdiagnosed with SPSD and unnecessarily exposed to immunotherapies. To address this, we studied patients evaluated at the Mayo Autoimmune Neurology Clinic with an outside diagnosis or suspicion of SPSD and compared clinical and ancillary testing characteristics of those deemed to have SPSD versus non-SPSD.

Methods

Patients provided informed consent for review of their electronic medical records (EMR) for research, and the study was approved by the Mayo Clinic Institutional Review Board (08–006647).

Patient identification and inclusion

The Mayo Data Explorer was used to search for patients whose records contained the terms "stiff person," "SPS," or "SPSD" and were evaluated in the Autoimmune Neurology Clinic (Mayo Clinic Rochester) from July 01, 2016, to June 30, 2021, by an Autoimmune Neurology Consultant (A.M., E.P.F, D.D., N.L.Z., S.J.P, A.Z.). The EMR of the identified patients was reviewed manually to determine whether they had been referred to Mayo Clinic with a suspected or previously established diagnosis of SPSD. We will use the term SPSD to define our cohort of classic or partial SPS or SPS-plus (including PERM and SPS with ataxia); pure cerebellar ataxia phenotype without SPS manifestations was excluded although previously suggested as part of SPSD.[6]

As there is no gold standard for SPSD diagnosis, we considered patients to have SPSD if that was the final diagnosis made by an autoimmune neurologist in our center and documented in the EMR. To strengthen diagnostic certainty, all patients also required either antibody positivity defined as presence of high-titer GAD65-IgG (≥20 nmol/L in serum by radioimmunoprecipitation assay or any positive titer in CSF), GlyR-IgG, amphiphysin-IgG (seropositive cohort), or abnormal electrodiagnostic studies compatible with SPSD. Electrodiagnostic studies included multichannel surface EMG with evaluation of auditory startle reflexes and exteroceptive responses,[14,23,24] and concentric-needle studies were performed on the paraspinal muscles. Agonist–antagonist co-contraction is not a component of the standard electrodiagnostic evaluation of SPSD at our institution (that includes, as mentioned above, the auditory startle reflexes, exteroceptive responses, and paraspinal muscle EMG), even though broadly available elsewhere, as it can also be seen in other neurologic conditions. Patients were designated as seropositive if they met the serologic criteria described, or seronegative if they only had abnormal electrodiagnostic studies. In order to increase diagnostic certainty, patients who were diagnosed with SPSD but did not meet the above serologic or electrodiagnostic criteria were excluded from analysis. In addition, patients were excluded if they were seen only by telemedicine or if definitive differentiation of SPSD from non-SPSD was not documented (Fig. 1). Alternative diagnoses were recorded for the non-SPSD patients, as documented by the autoimmune neurologist based on their evaluation of the patient's clinical presentation, examination, and paraclinical test findings.

The EMR was reviewed for demographic information, clinical presentation (stiffness, spasms, exaggerated startle [with anxiety, sound or tactile stimuli], unexplained falls, anxiety, or depression), comorbidities (cancer, other autoimmune disorders, excessive alcohol use [>2 drinks/day]), family history of autoimmunity, examination findings, investigation results, and therapeutic responses. Examination data extracted included tone and reflexes (dichotomized to increased or not), lumbar spine examination, and bedside exaggerated startle. The presence or absence of neuropathic signs, other movement disorders, functional neurologic signs, and widespread myofascial tenderness was noted. Mobility status at baseline and at last follow-up >1 year was recorded when available.

GAD65-IgG, GlyR-IgG, and amphiphysin-IgG were tested in the Mayo Clinic Neuroimmunology Laboratory as previously reported.[9,29–31] GAD65-IgG results of 3 patients who had abnormal testing by ELISA only and not repeated at Mayo by IPA were not included. CSF studies were considered abnormal in the presence of either an elevated white cell count (>5/μL) or ≥2 CSF-restricted elevated oligoclonal bands (cutoff defined by our laboratory as being abnormal). CSF protein was not evaluated due to lower specificity for CNS autoimmunity.

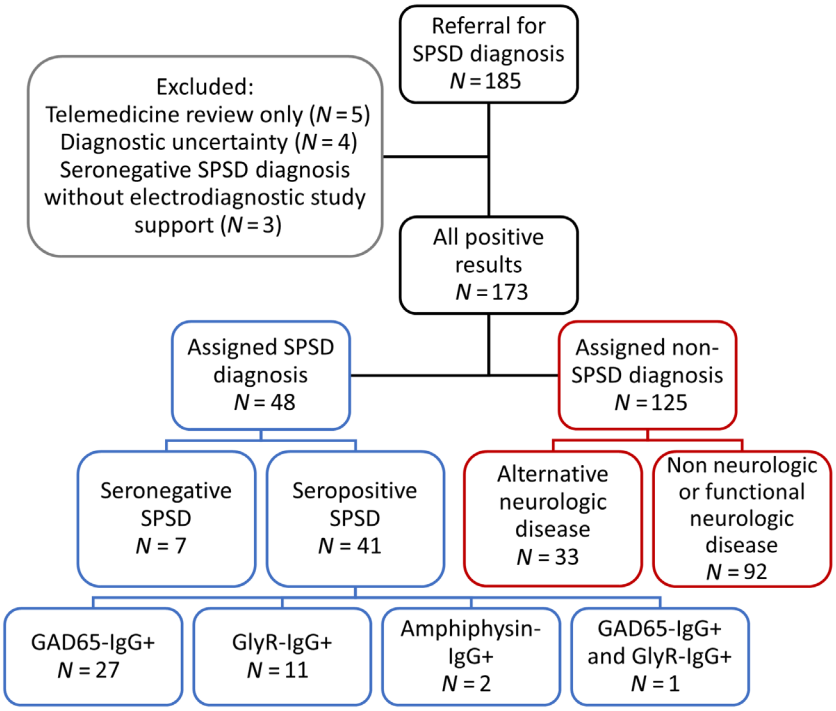

Figure 1. Patient population studied.

Treatment responses were categorized into one of three categories based on the physician's documentation of patient-described symptomatic benefit: no response (no or minimal improvement), moderate response (improvement but with definite residual symptoms and functional impairment), or excellent response (marked improvement with minimal residual symptoms or functional impairment). The usage and adverse effect rates of benzodiazepines (any type) and baclofen were assessed, as the most commonly encountered muscle relaxants. Maximum daily dose of benzodiazepine was recorded in diazepam milligram equivalents.

Statistical analysis

The statistics package used was R v4.0.3 (R Foundation for Statistical Computing, Austria). Univariate comparisons were performed using the Wilcoxon rank sum test for continuous variables and logistic regression for categorical variables (Fisher's exact was used when logistic regression was not possible). Patients were excluded from univariate analyses when the relevant data were missing. A p-value <0.05 was considered statistically significant. Multivariate logistic regression was limited by heterogeneous missing data in most patients and only select clinically relevant factors with statistical significance in univariate analysis were used; variables with excessive missing data were excluded.

Proposed diagnostic criteria

After the initial results, proposed diagnostic criteria for definite or probably stiff person syndrome were developed via consensus discussion between the authors.

Results

We included 173 patients; 48 (27.7%) were diagnosed with SPSD while the remainder were given non-SPSD diagnoses (125/173 [72.3%]). Neither median age (SPSD 47 [8–76] versus non-SPSD 51 [15–90], $p = 0.39$) nor female sex proportion (SPSD 68.8% versus non-SPSD 58.4%, $p = 0.21$) differed between groups.

SPSD patients

The majority of SPSD patients were seropositive

Of 48 SPSD patients, 41 (85.4%) were seropositive and 7 (14.6%) seronegative. The most common antibody in the seropositive cases was GAD65-IgG (28/41 [68.3%]) with median serum titer of 509.6 nmol/L (range 27–5179); 19/30 patients had elevated CSF GAD65-IgG (all were positive on serum testing). GlyR-IgG was present in serum in 10 patients, and in both serum and CSF in 2. One patient with high-titer GAD65-IgG also had serum GlyR-IgG. Two patients were positive for amphiphysin-IgG. None

were DPPX-IgG positive. Five of seven patients diagnosed with seronegative SPSD had low-titer serum GAD65-IgG (three <0.2 nmol/L, one at 1.2 nmol/L, and one 3.68 nmol/L). CSF pleocytosis was found in 5/34 patients (median 8, range 6–25, 4/5 lymphocytic predominant). Elevated CSF-specific oligoclonal bands were present in 12/32 (median 4.5, range 3–11); of those 10/12 were seropositive for GAD65-IgG and the other two were positive for amphiphysin-IgG. Oligoclonal bands were negative in all 5 GlyR-IgG SPSD patients tested. Electrodiagnostic studies were abnormal in 21/31 (68%) seropositive patients.

Insidious and progressive course with classic SPS phenotype was common

Most patients presented with a classic distribution of limb and truncal involvement (44/48 [92%]). Only two patients had stiff limb presentation alone and two presented with PERM both of whom were GlyR-IgG positive. The time course of presentation was insidious and progressive in most patients (45/48) while three reported an episodic course with extended periods of symptomatic remission followed by relapse.

SPS-plus had diverse phenotypes

Autoimmune neurologic overlap syndromes, some fulfilling the SPS-plus phenotypes described, occurred in 9/28 GAD65-IgG positive SPSD patients: myelopathy (4), ataxia (3), cognitive impairment and epilepsy (1) and ataxia, cognitive impairment, and epilepsy (1). One myelopathy patient with aquaporin-4-IgG positive neuromyelitis optical spectrum disorder had high-titer serum GAD65-IgG and additional clinical features consistent with SPSD. Five GlyR-IgG positive SPSD patients had additional neurologic involvement: PERM (2, mentioned above), ataxia (1), neuropathy (1), and neuropathy and cognitive impairment (1, without other features of PERM). One amphiphysin-IgG seropositive patient had additional myeloneuropathy. Confounding comorbidities occurred: chronic pain syndrome in three and functional neurologic disorders in three.

Autoimmune comorbidity was frequent while paraneoplastic association was uncommon

Other, non-neurologic autoimmunity occurred in 20/48 SPSD patients (42%) most commonly thyroid autoimmunity (13) and type 1 diabetes mellitus (7); 8 patients had more than one accompanying autoimmune condition. Malignancy was documented in three patients: breast cancer (amphiphysin-IgG-seropositive), seminoma (GlyR-IgG-seropositive), and colorectal cancer 4 years earlier (GAD65-IgG-seropositive).

SPSD patients commonly reported improvement with benzodiazepines

Most (40/48; 83%) SPSD patients received benzodiazepines; over half (18/35) had a moderate or marked response at a median diazepam equivalent dose of 40 mg (range 4–170). In contrast, only 3/30 (10%) reported moderate or excellent response to baclofen at a median dose 30 mg (range 10–120).

About half of SPSD patients reported clear benefit from immunotherapy

First-line immunotherapy (IVIg, steroids or PLEX) was used in the majority (42/48; 87.5%): 19/42 (45.2%) had at least moderate response. The most common immunotherapy was IVIg in 35 patients, followed by steroids in 20 and PLEX in 7. Second-line immunotherapy was prescribed in 20 patients. Most patients only received a single additional treatment: rituximab, 13; mycophenolate mofetil, 3; cyclophosphamide, 2. Only two patients had multiple second-line treatments (rituximab, cyclophosphamide and autologous hematopoietic stem cell transplantation, 1; azathioprine and rituximab, 1). Responses to second-line therapies were insufficiently documented and difficult to judge as they had commenced after already obtaining responses from first-line immunotherapy or benzodiazepines.

In 16 SPSD patients with >1 year follow-up, at a median of 2 years (range 1–5), 11 walked independently (69%), 3 required unilateral support, 1 bilateral support, and 1 required a wheelchair (at baseline 6 were walking independently, 3 required unilateral support, 3 bilateral support and 4 a wheelchair).

Non-SPSD clinical characterization

Most patients referred with suspicion or diagnosis of SPSD did not have that diagnosis

An alternative diagnosis was reached for 72.3% of patients referred for consideration of SPSD (Table 1). Alternative organic neurologic disease was found in 33/125 (26.4%) while non-neurologic or functional neurologic disease diagnoses were made in 92/125 (73.6%).

Almost all non-SPSD patients had chronic truncal and limb symptoms

The distribution of body symptoms involved limbs and trunk in 120/125 (96%) patients. Isolated limb involvement or isolated truncal involvement occurred in three

Table 1. Non-SPSD diagnoses.

Non-SPSD diagnosis	Number (N = 125)
Non-neurologic or functional neurologic disease	92 (73.6%)
Chronic pain syndrome and/or functional neurologic disease	81
Chronic pain alone	44
Functional neurologic disease alone	25
Both	12
Nonspecific somatic symptoms	11
Not immune-mediated neurologic disease	29 (23.2%)
Motor neuron disease	9
Other myelopathies	5
Parkinsonian syndrome	5
Neuropathy	4
Other movement disorders (hyperekplexia, post-anoxic spasticity, dystonia)	4
Other ataxias	1
Developmental neurologic disorder	1
Immune-mediated neurologic disease	4 (3.2%)
GAD65-IgG myelopathy and ataxia	1
GAD65-IgG ataxia	1
GlyR-IgG encephalomyelitis	1
Seronegative paraneoplastic encephalomyelitis	1

and two patients, respectively. Most patients had a history of chronic persistent symptoms (117/125), six had periods of remission and two had a paroxysmal course.

Most patients with SPSD misdiagnosis were seronegative or had low titers of GAD65-IgG

Serologic testing for these patients showed that 73/125 (58.4%) had detectable GAD65-IgG (median 0.15, range 0.03–959). Only six patients had GAD65-IgG titer ≥20 nmol/L, and 4/57 were positive on CSF (median 10.4, range 0.68–34.1). Two of them had alternative GAD65-IgG neurologic autoimmunity (both CSF GAD65-IgG positive), three had autoimmune thyroid disease and diabetes (one was CSF-IgG positive; CSF GAD65-IgG index not available), and one had chronic pain due to degenerative spine disease without stiff person phenomena and without known autoimmunity (also CSF GAD65-IgG positive with calculated CSF GAD65-IgG index 0.04). Three patients were positive for GlyR-IgG in serum (negative in CSF).[30] None were DPPX-IgG positive.

Chronic pain syndromes and functional neurologic disorders were the most common final diagnoses

Non-neurologic diagnoses, broadly classified as chronic pain disorders (many consistent with fibromyalgia), nonspecific somatic symptoms, or functional neurologic disorders were the most common final diagnoses (Table 1). The most common alternative organic neurologic diagnosis was motor neuron disease (9 cases), and there were several cases of parkinsonism, myelopathy, neuropathy, ataxia, and other movement disorders (Table 1).

Alternative autoimmune neurologic disorders were rare

Alternative autoimmune neurologic disorders occurred in only four patients: two cases of GAD65-IgG neurologic autoimmunity without SPSD, one case of GlyR-IgG encephalomyelitis (without features of SPSD and without cognitive change or myoclonus to meet criteria for PERM), and one case of seronegative paraneoplastic encephalomyelitis.

CSF abnormalities in non-SPSD patients generally had alternative explanations

CSF abnormalities in non-SPSD were attributable to other neurologic autoimmunity or pleocytosis secondary to IVIg, or were mild and nonspecific (3 oligoclonal bands in a patient with non-epileptic seizures and 2 oligoclonal bands in a patient with primary lateral sclerosis). A single patient with post-anoxic spasticity had mild pleocytosis (8 white blood cells/μL).

Non-SPSD patients frequently received benzodiazepines with limited efficacy

Non-SPSD patients were commonly prescribed benzodiazepines (92/125; 73.6%); 34 did not have a response documented. A moderate or excellent response was uncommon (9/58; 15.5%), at a median diazepam equivalent dose of 20 mg (range 2–240). While baclofen was commonly prescribed (75 patients), definite positive responses were rare (1/48 with moderate response). The median baclofen dose was 40 mg (range 5–120).

Non-SPSD patients were exposed to a significant immunosuppressive burden

Non-SPSD patients were commonly treated with immunosuppressive medication: 77/125 (61.6%) were exposed to at least one immunotherapy while 15 patients were exposed to 3 or more different immunotherapies (one patient underwent 5 different treatments). Immunotherapy responsiveness was poor in 59/68 patients with documented responses. Moderate symptomatic improvement occurred in 8 (none had autoimmune diagnoses) while a single patient with an eventual diagnosis of inflammatory

arthritis reported an excellent response after receiving steroids. Only 4/77 non-SPSD patients treated with immunotherapy had an alternative autoimmune neurologic diagnosis as a potential treatment indication; an additional patient had a prior diagnosis of myasthenia gravis that was in remission at time of evaluation.

Other autoimmunity occurred in 34/125 patients (27.2%) including thyroid autoimmunity (21) and type 1 diabetes mellitus (9).

Univariate comparison between SPSD and non-SPSD cohorts (Table 2)

Seropositivity for GAD65-IgG was more common in the SPSD cohort, especially in high titers (≥20 nmol/L in serum, odds ratio 24.5, $p < 0.001$).

Stiffness was ubiquitous among SPSD patients, and 95% reported additional muscle spasms; both symptoms were still described by the large majority of non-SPSD patients. When restricting for spasms triggered by tactile, auditory or emotional stimuli then they were more common in patients with SPSD. SPSD patients more frequently also reported a history of exaggerated startle response and unexplained falls. Presence of other personal autoimmunity was more common in SPSD. There was no difference between SPSD and non-SPSD patients relating to personal history of anxiety and/or depression or increased alcohol use.

Examination findings differed between groups: increased tone, hyperreflexia, exaggerated lumbar lordosis, and reduced lumbar spine range of motion were more common in patients with SPSD. Conversely, the myofascial tenderness or functional neurologic examination findings were more common in non-SPSD patients. An abnormal bedside examination startle response was found in similar proportions between groups, although documentation of this maneuver was infrequent.

Electrodiagnostic studies were more frequently abnormal in SPSD patients while the non-SPSD patients rarely had electrophysiological abnormalities; this included the electrophysiological acoustic startle and exteroceptive responses, and continuous paraspinal activity. Abnormal CSF studies were more common in SPSD patients.

SPSD patients were more likely to respond to benzodiazepines than non-SPSD patients. There was no difference between the maximal benzodiazepine dose, and no difference in the rate of reported adverse effects (SPSD 35% versus non-SPSD 26%, $p = 0.55$), most commonly mild sedation or cognitive change. Baclofen responsiveness, dose and adverse effect rate did not differ between groups.

Response to any immunotherapy was more common in SPSD patients. Immunotherapy response to specific regimens was better in SPSD patients despite relatively few patients exposed to each.

Multivariate analysis (Table 3)

Heterogeneous missing data limited the ability to explore many variables in multivariate analysis. With evaluating muscle spasms, unexplained falls, increased tone and/or hyperreflexia, myofascial tenderness and/or functional signs, any electrodiagnostic abnormality, and positive treatment response to immunotherapy (with either steroids, IVIg or PLEX), only 66 patients were included (20 SPSD and 46 non-SPSD). Among this group, the only variables that remained statistically different were the examination findings of either myofascial tenderness or functional neurologic signs (more common in non-SPSD), or the presence of any electrodiagnostic study abnormality (more common in SPSD).

Discussion

SPSD misdiagnosis is common

In this study, we found that misdiagnosis was threefold more common than SPSD diagnosis. This is often related to misinterpretation of neural antibody results, clinical signs, and symptoms misinterpreted as being SPSD-related or lack of electrophysiological assessments in patients suspected to have SPSD.[4,11] Even though GAD65-IgG is the most common neural antibody found in SPSD patients, it also occurs in patients with type 1 diabetes mellitus, thyrogastric autoimmunity, and normal health (often low-titer).[9–11] GlyR-IgG detection is also challenging as there is a risk for false positivity in serum and most SPSD patients (other than PERM), are CSF negative.[30] Finally, immunoblots used in isolation are prone to false positivity (e.g., for amphiphysin-IgG) and are better as confirmatory tests.[32,33] Due to reports of SPSD-like presentations in DPPX autoimmunity, we assessed this antibody in our cohort; however, no cases were identified.

SPSD diagnosis is challenging but several features aid accurate diagnosis

Clinically, exaggerated startle, stimuli-triggered spasms, unexplained falls, personal autoimmunity and abnormal limb and lumbar spine examination predict SPSD diagnosis. Conversely, myofascial tenderness or functional neurologic signs should raise suspicion for an alternative diagnosis, although a few SPSD patients had comorbid chronic pain or functional neurologic examination findings. Anxiety and depression found in more than half of

Table 2. Univariate analysis comparing SPSD with non-SPSD patients.

Variable	SPSD (%)	Non-SPSD (%)	Odds ratio (95% CI)	*p*-value
Serological findings				
Serum GAD65-IgG >0.02 nmol/L	36/48 (75)	59/111 (53)	2.64 (1.27–5.79)	**0.011**
Serum GAD65-IgG ≥20 nmol/L	28/48 (58)	6/111 (5)	24.50 (9.54–72.74)	**<0.001**
Serum/CSF GlyR-IgG positive	12/35 (34)	3/40 (8)	6.44 (1.82–30.51)	**0.008**
Historical symptoms				
Stiffness	48/48 (100)	99/110 (90)	NA	**0.035**
Any spasms	41/43 (95)	87/108 (81)	4.95 (1.36–31.9)	**0.036**
Spasms with trigger[1]	24/38 (63)	26/73 (36)	3.10 (1.39–7.14)	**0.007**
Exaggerated startle	30/37 (81)	35/62 (56)	3.31 (1.31–9.22)	**0.015**
Sound trigger	21/38 (55)	27/65 (42)	1.74 (0.78–3.94)	0.18
Tactile trigger	4/38 (11)	6/65 (9)	1.16 (0.28–4.34)	0.83
Anxiety trigger	12/38 (32)	13/65 (20)	1.85 (0.74–4.64)	0.19
Unexplained falls	34/45 (76)	43/94 (46)	3.67 (1.70–8.39)	**0.001**
Background history				
Personal history autoimmunity	24/48 (50)	34/125 (27)	2.68 (1.35–5.37)	**0.005**
Family history autoimmunity	22/48 (46)	43/125 (34)	1.61 (0.82–3.18)	0.17
Anxiety	22/38 (58)	53/94 (56)	1.06 (0.50–2.30)	0.87
Depression	17/38 (45)	51/94 (54)	0.68 (0.32–1.45)	0.32
Increased alcohol use	4/46 (9)	6/123 (5)	1.86 (0.46–6.82)	0.36
Examination findings				
Increased tone	29/48 (60)	30/124 (24)	4.78 (2.38–9.87)	**<0.001**
Hyperreflexia	34/48 (71)	53/124 (43)	3.25 (1.61–6.83)	**0.001**
Exaggerated lumbar lordosis	24/36 (67)	7/75 (9)	19.43 (7.20–58.89)	**<0.001**
Reduced lumbar spine range of movement	11/25 (44)	6/43 (14)	4.85 (1.55–16.54)	**0.008**
Abnormal bedside startle response	7/18 (39)	10/54 (19)	2.80 (0.85–9.10)	0.085
Neuropathic findings	3/48 (6)	17/125 (14)	0.42 (0.10–1.34)	0.19
Other movement disorder	8/48 (17)	10/125 (8)	2.30 (0.83–6.24)	0.10
Myofascial tenderness	3/48 (6)	28/125 (22)	0.23 (0.05–0.70)	**0.021**
Functional neurologic findings	3/48 (6)	41/125 (33)	0.14 (0.03–0.40)	**0.001**
Investigations				
Any electrodiagnostic abnormality	28/38 (74)	16/96 (17)	14.00 (5.89–35.95)	**<0.001**
MDL abnormal acoustic startle response	22/38 (58)	12/80 (15)	7.79 (3.27–19.57)	**<0.001**
MDL abnormal exteroceptive responses	22/37 (59)	5/79 (6)	21.71 (7.60–73.54)	**<0.001**
EMG continuous paraspinal activity	10/32 (31)	4/69 (6)	7.39 (2.23–29.18)	**0.002**
Abnormal CSF	15/34 (44)	9/64 (14)	4.83 (1.85–13.27)	**0.002**
Treatment				
Benzodiazepine response at least moderate[2]	18/35 (51)	9/58 (16)	5.77 (2.24–15.85)	**<0.001**
Benzodiazepine maximal dose ≥30 mg/day	20/37 (54)	37/88 (42)	1.62 (0.75–3.54)	0.22
Baclofen response at least moderate[3]	3/30 (10)	1/48 (2)	5.22 (0.63–108.45)	0.16
Baclofen maximal dose ≥30 mg/day	26/32 (81)	55/73 (75)	1.42 (0.53–4.29)	0.51
Immunotherapy response at least moderate	19/42 (45)	9/68 (13)	5.42 (2.20–14.26)	**<0.001**
Steroid response, at least moderate	8/20 (40)	2/32 (6)	10.00 (2.14–73.05)	**0.008**
IVIg response, at least moderate	12/32 (38)	8/53 (15)	3.38 (1.21–9.87)	**0.022**
PLEX response, at least moderate	3/7 (43)	0/13 (0)	NA	**0.031**

$p < 0.05$ values are in bold fond (statistically significant).

CSF, cerebrospinal fluid; DPPX, dipeptidyl-peptidase-like protein-6; EMG, electromyography; GAD65-IgG, glutamic acid decarboxylase 65 kilodalton isoform antibody; GlyR-IgG, glycine receptor alpha-1 subunit antibody; IVIg, intravenous immune globulin; MDL, movement disorder laboratory; PLEX, plasma exchange; SPSD, stiff person spectrum disorder.

[1]Triggers to sound, tactile stimulus or anxiety.

[2]Benzodiazepine median maximal dose was 10 mg (range 4–170) for SPSD and 20 mg (range 2–240 mg) for non-SPSD ($p = 0.08$).

[3]Baclofen median maximal dose was 30 mg (range 10–120) for SPSD and 40 mg (range 5–120 mg) for non-SPSD ($p = 0.92$).

the patients were present in similar frequencies between SPSD and non-SPSD. While chronic pain syndromes and functional neurologic diagnoses might predict a higher prevalence of anxiety and depression, it is well recognized that anxiety and phobias are prevalent among patients with GAD65-IgG-positive SPSD.[4,28,34]

Table 3. Multivariate analysis (SPSD $N = 26$, non-SPSD $N = 40$).

Variable	Odds ratio (95% CI)	Multivariate *p*-value
Spasms	3.56 (0.50–72.98)	0.272
Unexplained falls	2.12 (0.55–8.27)	0.270
Increased tone or reflexes	2.13 (0.41–12.81)	0.379
Myofascial tenderness or functional neurologic signs	0.22 (0.05–0.84)	**0.034**
Any electrodiagnostic abnormality	7.08 (1.65–36.09)	**0.011**
Immunotherapy response, at least moderate	1.60 (0.30–8.09)	0.568

$p < 0.05$ values are in bold fond (statistically significant).

Serological, neurophysiological, and CSF testing are critical ancillary tests

In a patient with clinical suspicion of SPSD, antibody positivity remains a critical diagnostic biomarker. Neurophysiological findings and CSF analysis can be supportive for the diagnosis. Practically, EMG of paraspinal muscles for continuous motor unit activity should be performed in all patients, and abnormal results would be anticipated in those with truncal involvement.[8] Electrophysiological evaluation of co-contraction of agonist/antagonist muscles is also useful in the right clinical context but can be seen in dystonia and functional disorders as well.[35,36] Acoustic startle and exteroceptive responses when both are clearly abnormal have high specificity for SPSD. However, these tests are only available at few institutions internationally and have limited sensitivity in patients taking benzodiazepines; validation of age- and sex-normalized cutoffs for these tests is still needed.[14,23,24]

Suggested SPSD diagnostic criteria

Given our findings, we proposed a set of diagnostic criteria based on clinical presentations, examination findings, and serological and electrophysiological testing (Table 4) that will need to be evaluated prospectively. The clinical experience of the authors and attempts to generalize criteria for use in other centers with different electrophysiological or serological studies available led to inclusion of concurrent stiffness of lumbar paraspinal and abdominal muscles by examination, high-titer seropositivity by GAD65-IgG ELISA, and agonist–antagonist contraction by EMG, which was not performed in this study but as a more broadly available test will be important for prospective studies. We excluded hyperreflexia that was one of the significant examination differentiators in our cohort as it was deemed of lower specificity than increased tone and can be seen in normal individuals; we did not analyze segmental hyperreflexia (generalized versus upper or lower limbs or jaw jerk) which could have more discriminative value. When applied to our current cohort with available clinical information (Table 5), all SPSD patients would fulfill criteria for definite or probable diagnosis. Conversely, none of the non-SPSD would meet criteria for definite diagnosis and 12 would meet criteria for probable SPSD (sensitivity 100%, specificity 89%), excluding criterion 5 (all non-SPSD patients in our cohort had an alternative diagnosis). The performance of these criteria needs to be validated in a prospective multi-center study.

Table 4. Proposed diagnostic criteria for stiff person syndrome.

1 Clinical—Symptoms (1 of 2)
   a Stiffness (axial regions, limbs, or both)
   b Episodic spasms (axial regions, limbs, or both) triggered by noises, tactile stimuli, emotional stress
2 Clinical—Signs during symptomatic phase of illness (1 of 3)
   a Increased muscle tone (axial or limb)
   b Exaggerated lumbar lordosis
   c Concurrent stiffness of lumbar paraspinal and abdominal muscles
3 Serological findings (1 of 3)
   a High-titer GAD65-IgG in the serum (≥20 nmol/L by radioimmunoprecipitation assay or 10,000 IU/mL by ELISA) or any positive titer in CSF
   b Glycine-R-IgG in serum and/or CSF by live cell binding assay
   c Amphiphysin-IgG in serum and/or CSF by immunohistochemistry and antigen-specific assay as confirmation
4 Electrophysiological studies (1 of 3)
   a Inability to relax paraspinal muscles in needle EMG
   b Exaggerated acoustic or exteroceptive responses by surface EMG
   c Co-contraction of agonist/antagonist muscles by EMG
5 Exclusion of alternative diagnosis

Definite: All (1–5). **Probable:** At least one of #1 or #2 AND #3 AND #5 (seropositive). **OR** #1, #2, #4 and #5 (seronegative).

Table 5. Diagnostic classification using proposed criteria[1]

Diagnostic classification	SPSD, $N = 48$ (%)	Non-SPSD, $N = 110$ (%)[2]
Definite SPSD	15 (31)	0 (0)
Probable SPSD	33 (69)	12 (11)[3]
Seropositive	26 (54)	7 (6)[4]
Seronegative	7 (15)	5 (5)
Not meeting SPSD criteria	0 (0)	98 (89)

[1]Does not consider Criterion 5.
[2]15 patients were excluded from being assessed for diagnostic criteria due to missing data.
[3]All had alternative diagnoses identified.
[4]4 had alternative autoimmune neurologic diagnoses.

Immunotherapy and benzodiazepine responses are more common in SPSD

Treatment responses are variable but favor better results among SPSD patients treated with benzodiazepines and/or immunotherapy. Treatment responses especially to benzodiazepines alone should be assessed with objective clinical data. SPSD misdiagnosis should be considered in patients without significant benefit from immunotherapy and diagnosis reevaluation should occur prior to additional trials of immunosuppressive medications or autologous hematopoietic stem cell transplantation. Indeed, this study demonstrated that patients without SPSD were sequentially exposed to up to 5 immunosuppressive therapies in the absence of neurologic autoimmunity. Aside from cost, this unwarranted treatment impairs vaccine responses and increases the risk of severe infection and malignancy. Harm also arises when SPSD misdiagnosis leads to non-management of the undiagnosed disorder: non-neurologic, functional neurologic, and alternative neurologic disorders benefit from targeted care that usually does not entail immunosuppression. Accurate diagnosis also minimizes the inefficient use of patient and healthcare resources.

Study limitations

There are limitations to this study. While many variables were statistically significant in univariate analysis, the incomplete dataset due to the retrospective nature of this study restricted the ability to perform multivariate analysis. However, the univariate analysis still provides clinically useful information. In addition, the standard for inclusion in this study was based on the opinion of an autoimmune neurologist at Mayo Clinic, a quaternary referral center with considerable experience diagnosing and managing patients with SPSD. This study did not evaluate patients with GAD65-IgG seropositivity judged by ELISA which may be more readily available in some areas, although a serum cutoff of >10,000 IU/mL has been established as predictive of neurologic autoimmunity in previous studies and thus included in the diagnostic criteria.[11] In addition, the cutoff value of 20 nmol/L for GAD65-IgG in the serum tested by radioimmunoprecipoitation assay in our laboratory was established previously as being more readily associated with neurologic autoimmunity and was used for this study; lower titers of GAD65-IgG may still have biological and pathophysiological significance for SPSD.[9]

We further stipulated the need for seropositivity or supportive electrodiagnostic studies to increase diagnostic certainty; however, there is no diagnostic gold standard for confirming SPSD. A minority of seropositive SPSD patients had normal electrodiagnostic studies that could be related to imperfect test thresholds or protocols (e.g., suppression of elicitable CNS hyperexcitability by benzodiazepines), raising concerns about missing seronegative SPSD patients in our cohort. From the 185 patients that were reviewed in our center, only 3 seronegative patients had a final diagnosis of SPSD without electrophysiological evidence of SPSD (Fig. 1, patients were excluded for the analysis). On the contrary, the non-SPSD patients in our cohort had alternative diagnosis and their clinical presentation and examination were not compatible with SPSD based on the autoimmune neurologist's review. Given the rarity of seronegative SPSD, stricter diagnostic criteria are necessary to prevent overdiagnosis which is the reason why electrophysiological abnormalities were included in the criteria for the seronegative patients. Electrodiagnostic testing for SPSD is not universally available, and refinement of abnormal thresholds may improve test accuracy, which is of particular importance for the minority of seronegative SPSD cases. In our cohort we did not evaluate the diagnostic performance of agonist/antagonist co-contraction by electrophysiology that is more readily available in other centers but due to existing literature this was included in the criteria.

In addition, patients seen at Mayo Clinic are often those who have failed initial immunotherapy or who are self-referred, creating bias toward patients with SPSD misdiagnosis; while this detracts from the generalizability of the misdiagnosis rate to other centers, the very high rate of misdiagnosis and the high prevalence of alternative diagnoses (functional neurologic disorder, chronic pain syndromes) suggest that awareness of SPSD misdiagnosis is still critical. Few patients had extended longitudinal follow-up, limiting the ability to evaluate long-term responsiveness to first-line or second-line immunotherapy, which may be important as SPSD disability may progress despite initial apparent response to immunotherapy.[37] Subjective symptom rating may not truly reflect biological improvement, and objective treatment response measurement will be important in future studies. Finally, we have not tested for other neural antibodies described with SPSDsuch as gephyrin-IgG, but these antibodies are exceedingly rare.[7,19–22]

Conclusions

In conclusion, we demonstrate that misdiagnosis of SPSD is common and we identify key features in the patients' presentation, ancillary testing, and treatment response that aid SPSD diagnosis. This will facilitate early and appropriate treatment for patients suspected of SPSD and minimize inappropriate and potentially harmful administration of immunotherapies to patients without an autoimmune disorder. Patients with a normal neurologic examination, normal electrodiagnostic studies (when

Table 6. Red flags to consider SPSD misdiagnosis.

Presentation
Stiffness and spasms are absent, or not a major symptom
Muscle symptoms are atypical for SPSD-related spasms[1]
Chronic pain syndrome is the predominant feature
Absence of increased tone
Normal lumbar spine examination in those with truncal symptoms
Prominent lower motor neuron findings, including muscle wasting or fasciculations
Presence of prominent myofascial tender points
Functional neurologic signs[2]
Ancillary testing
Absence of serum or CSF antibodies associated with SPSD (high-titer GAD65-IgG, GlyR-IgG, amphiphysin-IgG)
Normal paraspinal EMG for patients with truncal involvement
Normal acoustic startle and exteroceptive responses by surface EMG, when available[3]
Clinical course
No objective improvement with benzodiazepines
No objective improvement with immunotherapy

[1]Involving contraction of isolated muscle groups (cramps) rather than agonist–antagonist pairs, or symptoms not triggered by sound, tactile stimulus or emotional stress.

[2]May include give-way weakness, functional gait disorders and witnessed non-epileptic episodes.

[3]Patients treated with benzodiazepines may have false negative results.

available), minimal benefit with first-line immunotherapy, and low-titer GAD65-IgG or absent relevant serological positivity should be re-evaluated for alternative diagnoses (red flags, Table 6). While this study provides useful information about factors differentiating SPSD from alternative disorders and we suggest diagnostic criteria based on our findings, further study is required to validate these criteria, including electrophysiological criteria, that will aid widespread accurate diagnosis of SPSD and assist in accurate patient selection for future therapeutic trials.

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Author Contributions

Chia and Zekeridou involved in conception and design, and drafting of manuscript and figures. All authors involved in acquisition and analysis of data.

Conflict of Interest

Drs Chia, Klassen, Zalewski, and Mr Duffy report no relevant disclosures. Dr McKeon reports patent applications issued for MAP1B and GFAP-IgGs and pending for Septin-5, PDE10A, Kelchl11-IgGS as biomarkers of autoimmune neurologic disease. He has consulted for Grifols, Medimmune, and Euroimmun; and received research support from Grifols, Medimmune, Alexion, and Euroimmun but has not received personal compensation. He also received research funding from the NIH (NIH: RO1NS126227, U01NS120901). He is working as a consultant in the Mayo Clinic Neuroimmunology laboratory clinical service that offers commercial neural antibody testing, but revenue accrued does not contribute to salary, research support, or personal income for any of the authors. Dr Dalakas has consulted or served on a Scientific Advisory or Data Safety Monitoring board for Alexion, Grifols, Argenx, Sanofi, Octapharma, Takeda/Hyquvia, and the Dysimmune Diseases Foundation and has received personal compensation. He serves as an editor, associate editor, or editorial advisory board member for the AAN and Elsevier. Dr Flanagan has served on advisory boards for Alexion, Genentech, and Horizon Therapeutics. He has received speaker honoraria from Pharmacy Times. He received royalties from UpToDate. Dr Flanagan was a site primary investigator in a randomized clinical trial on Inebilizumab in neuromyelitis optical spectrum disorder run by Medimmune/Viela-Bio/Horizon Therapeutics. Dr Flanagan has received funding from the NIH (R01NS113828). Dr Flanagan is a member of the medical advisory board of the MOG project. Dr Flanagan is an editorial board member of the Journal of the Neurologic Sciences and Neuroimmunology Reports. A patent has been submitted on DACH1-IgG as a biomarker of paraneoplastic autoimmunity. He is working as a consultant in the Mayo Clinic Neuroimmunology laboratory clinical service that offers commercial neural antibody testing, but revenue accrued does not contribute to salary, research support, or personal income for any of the authors. Dr Bower reports research funding from Novartis and Transposon. Dr Dubey reports patents pending for the KLHL11 and LUZP4-IgGs as markers of neurologic autoimmunity and germ cell tumor. He has served on advisory board for UCB and has been a consultant for Immunovant and Astellas. He is working as a consultant in the Mayo Clinic Neuroimmunology laboratory clinical service that offers commercial neural antibody testing, but revenue accrued does not contribute to salary, research support, or personal income for any of the authors. Dr Pittock reports grants, personal fees, and non-financial support from Alexion Pharmaceuticals, Inc.; grants, personal fees, non-financial support, and other support from MedImmune, Inc/Viela Bio.; personal fees for consulting from Genentech/Roche, UCB and Astellas. He has patent issued related to functional AQP4/NMO-IgG assays, NMO-IgG as a cancer marker and MAP1B-IgG and

GFAP-IgG as a biomarker of Neurologic Autoimmunity. Dr Pittock also has patents pending for the following IgGs as biomarkers of autoimmune neurologic disorders (septin-5, kelch-like protein 11, DACH1, LUZP4). He is working as a consultant in the Mayo Clinic Neuroimmunology laboratory clinical service that offers commercial neural antibody testing, but revenue accrued does not contribute to salary, research support, or personal income for any of the authors. Dr Zekeridou has patents pending for PDE10A and DACH1-IgG as biomarkers of neurologic autoimmunity, has received research funding from Roche/Genentech, and has consulted for Alexion pharmaceuticals but has not received personal compensation. She is working as a consultant in the Mayo Clinic Neuroimmunology laboratory clinical service that offers commercial neural antibody testing, but revenue accrued does not contribute to salary, research support, or personal income for any of the authors.

Data Availability Statement

Anonymized data will be shared by the corresponding author on reasonable request.

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